REMARKS

Status of the Claims

Claims 1, 10 and 13-14 have been amended; Claims 8 and 9 have been canceled; and Claims 23-24 have been added.

Claim 1 has been amended to recite that the composition includes "glycine." Support for the amendment can be found, for example, on page 3, line 14, to page 4, line 25; page 10, lines 1-7; and in Examples 1-3, of the Specification. Claim 1 also has been amended to recite that "glycine is present at a concentration of about 0.5% to about 5%." Support for the amendment can be found, for example, on page 10, lines 5-7; and in Examples 1-3, of the Specification. Claim 1 further has been amended so that "at least one reducing agent" is now "dithiothreitol (DTT)." Support for the amendment can be found, for example, in original Claim 9. Accordingly, no new matter has been introduced by way of these amendments.

In view of the amendments to Claim 1, Claims 8 and 9 have been canceled.

Because Claim 9 has been canceled, Claims 10 and 13 have been amended to depend from Claim 1. Likewise, Claim 14 has been amended to depend from new Claim 23. Accordingly, no new matter has been introduced by way of these amendments.

New Claim 23 has been added, which recites that the claimed composition "further comprises n-acetyl-cysteine." Support for new Claim 23 can be found, for example, in original Claim 9. Accordingly, no new matter has been introduced by way of new Claim 23.

Claims 1-7, 10-14 and 23 therefore are pending in the application and are under examination. Reexamination and reconsideration are respectfully requested.

Applicants respond to the objection and the rejections below as they are set forth in the Office Action.

Restriction Requirement

On March 6, 2009, Applicants' representative elected Group I (Claims 1-14) in a Response to Requirement for Restriction. The Examiner made the restriction final. Consequently, Claims 15-22 are hereby withdrawn from prosecution.

The Objection to the Specification Should Be Withdrawn

The Specification was objected to for having embedded hyperlinks and/or other forms of browser-executable code. The Specification has been amended to delete the embedded hyperlink on page 16. In view of the amendment, Applicants respectfully request that the objection be withdrawn.

The Rejection Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 1-13 were rejected under 35 U.S.C. § 102(b) as anticipated by US Patent No. 5,714,458 to Adami *et al.* The rejection is respectfully traversed.

The claimed invention relates to stabilized liquid or lyophilized pharmaceutical compositions comprising (1) fibroblast growth factor (FGF) or a variant thereof, (2) glycine, and (3) dithiothreitol (DTT) in an amount sufficient to inhibit oxidation of the FGF or variant thereof. In addition, the pharmaceutical compositions can comprise n-acetyl-cysteine.

Adami *et al.* generally disclose lyophilized compositions having (1) FGF, (2) a bulking agent and either (3) an alkali metal salt of a carboxyalkyl cellulose or (4) a polyoxyethylene sorbitan fatty acid ester and cysteine. Adami *et al.* also disclose a lyophilized composition further having a "suitable concentration" glycine as a lyoprotectant (Column 6, lines 43-54).

The Adami *et al.* reference, however, cannot anticipate the claimed invention because it does not teach a suitable range of glycine in the composition. To be anticipatory, a prior art reference must not only disclose the claimed invention as arranged in the claims, but must also "enable one of ordinary skill in the art to make the invention without undue experimentation." *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 545 F.3d 1312, 1314 (Fed. Cir. 2008). As such, a prior art reference is enabling under § 102 when it teaches one of skill in the art how to "make" a composition or how to "use" a method, although it not need disclose an independent use or utility to anticipate. *See*, *In re Glevave*, No. 2008-1453 (Fed. Cir., decided March 26, 2009).

Here, Adami *et al.* do not teach one of skill in the art how to make the claimed invention. For example, while Adami *et al.* disclose that a "suitable concentration" (Column 6, lines 47-52) of glycine was used in its lyophilized compositions, the reference does not disclose what that concentration actually was or what range that concentration could be. More importantly, Adami *et al.* also disclose that "PVA, sodium chloride, glycine and albumin proved to be highly

incompatible with bFGF" (emphasis added) (*see*, Column 6, lines 66-67). Accordingly, the concentration of glycine used by Adami *et al*. did not result in a composition that could be used as their findings would indicate that glycine cannot be used with bFGF.

In contrast, the claimed invention relates to liquid or lyophilized compositions in which glycine is compatible with FGF, particularly when the glycine is present at a concentration of about 0.5% to about 5%. Because Adami *et al.* do not teach this range, it cannot anticipate the claimed invention. In view of the amendments above and remarks herein, Applicants respectfully request that the rejection be withdrawn.

The Rejections Under 35 U.S.C. § 103 Should Be Withdrawn

Claims 4 and 5 were rejected under 35 U.S.C. § 103(a) as obvious over Adami *et al.*, *supra*, in view of US Patent No. 6,165,981 to Flaa *et al.* The rejection is respectfully traversed.

As noted above, the claimed invention relates to stabilized liquid or lyophilized pharmaceutical compositions comprising (1) fibroblast growth factor (FGF) or a variant thereof, (2) glycine and (3) dithiothreitol (DTT) in an amount sufficient to inhibit oxidation of the FGF or variant thereof. In addition, the pharmaceutical compositions can comprise n-acetyl-cysteine.

The Adami *et al.* reference is summarized above. Briefly, Adami *et al.* generally disclose lyophilized compositions having FGF, but teach away from using glycine because it is "highly incompatible" with FGF.

Flaa *et al.* generally disclose compositions and methods for stabilizing proteins, especially cardiac marker proteins, with (1) a buffer, (2) a stabilizing protein such as albumin, ovalbumin or casein, (3) a chelating agent such as EGTA, EDTA, sodium citrate or an oxalate salt, (4) a reducing agent such as N-acetyl-cysteine, 2-aminoethanethiol, 2-mercaptoethanol, 2-mercaptoethylanine or DTT, and (5) a salt (Columns 4-5). Flaa *et al.* also disclose the use of a protease inhibitor, detergents and/or preservatives (Column 5, lines 32-56). Flaa *et al.*, however, do not contemplate or disclose compositions having FGF and glycine.

Recently, the Supreme Court identified seven (7) rationales for use in supporting obviousness determinations, which are consistent with the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), which provides a framework for applying the statutory language of § 103 (*i.e.*, the "Graham Factors"). *See*, *KSR International Co. v. Tele-flex Inc.*, 550

U.S. 389 (2007); and MPEP § 2143. Regardless of the applied rationale, prior art "can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success." MPEP § 2143.02 I. The reasonable expectation of success is not required to be absolute (MPEP § 2143.02 II.), but must be determined at the time the invention was made (MPEP § 2143.02 III.). Thus, "evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness." MPEP § 2143.02.

One of skill in the art had no reasonable expectation of success in arriving at the claimed invention by combining Adami *et al.* and Flaa *et al.*. A reasonable expectation of success presupposes that one of skill in the art is capable of predicting before a research project is initiated – rationally and on the basis of existing knowledge – the successful conclusion of the project within an acceptable time limit.

Here, Adami *et al.* do not provide any guidance on what a "suitable concentration" of glycine can be in a lyophilized composition having FGF. More importantly, the reference teaches away from using glycine with FGF, as glycine was "highly incompatible" with FGF.

The Flaa *et al.* reference does not bridge the gaps between Adami *et al.* and the claimed invention because it contains no mention of glycine at all. One of skill in the art therefore had no reasonable expectation of success in arriving at the claimed invention by combining Adami *et al.* and Flaa *et al.* Moreover, a combination of Adami *et al.* and Flaa *et al.* does not result in the claimed invention because such a composition would not have glycine. As such, a combination of Adami *et al.* and Flaa *et al.* cannot render obvious the claimed invention. In view of the amendments above and remarks herein, Applicants respectfully request that the rejection be withdrawn.

Conclusion and Fees

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the objection to the Specification, the anticipation rejection and the obviousness rejection are overcome. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited.

A petition for a three-month extension of time accompanies this response so that it will be deemed to have been timely filed. No other extension of time is believed due; however, if any

additional extension is due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 16-0605. Likewise, no additional fees such as for net addition of claims are believed due; however, if any fees are due, in this or any subsequent response, please charge Deposit Account No. 16-0605.

Respectfully submitted,

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